

Please substitute the enclosed sections entitled "5.3 EXAMPLE 3 – DEVELOPMENT AND TESTING OF RIBOZYME TARGETING A_{2B} ADENOSINE RECEPTOR mRNA" for the corresponding section originally submitted with the application as filed.

Please substitute the enclosed TABLE 4, TABLE 5 and TABLE 6 for the corresponding tables originally submitted with the application as filed.

After page 111, please insert the Sequence Listing that is enclosed herewith.

REMARKS

The above amendments are for the purpose of correcting the drawing descriptions, correcting some of the tables, and inserting the sequence listing.

Should any fees under 37 C.F.R. §§ 1.16 to 1.21 be required for any reason, the Assistant Commissioner is authorized to deduct said fees from Williams, Morgan & Amerson, P.C. Deposit Account No. 50-0786/4300.014100.

Please date stamp and return the accompanying postcard to evidence receipt of these documents.

Respectfully submitted,



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3. BRIEF DESCRIPTION OF THE DRAWINGS

The following drawings form part of the present specification and are included to further demonstrate certain aspects of the present invention. The invention may be better understood by reference to the following description taken in conjunction with the accompanying drawings, in which like reference numerals identify like elements, and in which:

FIG. 1 shows adenosine, acting through its type A_2 receptor, can act to increase oxygen supply via two paths. During acute hypoxia, adenosine acts on smooth muscle cells, resulting in vasodilation (A_{2A}). With chronic ischemia, adenosine acts as an angiogenic agent by exerting a mitogenic effect on microvascular endothelial cells (in HREC, A_{2B} ; see below). It is this latter effect that can be interfered with in an attempt to develop a pharmacological therapy for neovascular diseases. A distinct receptor subtype that mediates solely the mitogenic effect of adenosine would allow the targeting of a selective antagonist against that receptor subtype, without preventing the vasodilation mediated by the A_{2A} receptor;

FIG. 2A shows HREC proliferation after stimulation with NECA alone or in combination with a blocking antibody to VEGF. Open bars are results after 24 hr of exposure; filled bars are results after 48 hr. (*), significantly different from 10 μ M NECA alone for the respective exposure time by ANOVA ($p < 0.05$). Also shown are control cells exposed to VEGF alone or in combination with anti-VEGF to demonstrate the efficacy of the antibody;

FIG. 2B shows VEGF content in conditioned medium from HREC after stimulation with NECA in the presence or absence of sense or antisense oligonucleotides homologous to human A_{2B} adenosine receptor or to human VEGF. Assay duration was 48 hr. A_{2B} antisense treatment reduces the amount of VEGF protein secreted in response to NECA to levels equaling or exceeding the reduction evident by VEGF antisense treatment;

FIG. 3A and **FIG. 3B** show NECA, at the concentrations indicated in the legends, induces a transient activation of ERK/MAPK in HREC that peaks at 5 min and desensitizes by 20 min after exposure. HREC were serum-starved for 24 hr and pre-treated for 20 min with 1 U/mL adenosine deaminase prior to adding NECA. Activated ERK/MAPK was visualized on Western blots by enhanced chemiluminescence using EC10 monoclonal antibody;

FIG. 4A, **FIG. 4B** and **FIG. 4C** show the A_1 -selective agonist CPA stimulates ERK/MAPK phosphorylation in HREC, however the A_{2A} -selective agonist CGS did not activate ERK/MAPK;

FIG. 5 shows HREC were pretreated for 30 min with the MEK inhibitor PD98059 or the PKA inhibitor H-89 and stimulated with NECA for 5 min. PD98059 inhibited ERK activation, while H-89 increased basal ERK activation. H-89 did not block NECA-stimulated ERK activation, suggesting that PKA is not involved in signaling from the adenosine receptor to ERK. The non-selective adenosine receptor antagonist XAC decreased ERK activation by high concentrations of NECA, but modestly increased ERK activation in control conditions and in response to 1 and 10 nM NECA. In contrast, PD98059 did not alter CREB, whereas both H-89 and XAC blocked NECA-induced CREB activation. These data indicate that NECA results in ERK activation independent of the cAMP response;

FIG. 6 shows both Enprofylline and JW V-108 antagonize activation of p42 and p44 ERK/MAP kinase by NECA. HRECs were serum-starved for 24 hr and pre-treated with adenosine deaminase (ADA, 1 U/mL) for 20 min, incubated with the antagonists in the presence of ADA for 10 min. NECA (1 nM-10 μ M, 10 min) was used to activate ERK. ERK activation was analyzed by Western blot using the E10 monoclonal antibody, which recognizes the phosphorylated (active) form of the enzyme;

FIG. 7A, **FIG. 7B** and **FIG. 7C** show a schematic representation (**FIG. 7A**) of the A_{2B} adenosine receptor ribozyme showing the nucleotide sequence of the recognition arms (SEQ ID NO:1), as well as the complementary sequence of the synthetic target (SEQ ID NO:2). Cleavage of this target by the ribozyme is shown in the autoradiogram (**FIG. 7B**), demonstrating the cleavage kinetics. Band densities of cleaved vs. intact target were plotted as percent cleaved (**FIG. 7C**). The A_{2B} receptor ribozyme cleaves nearly 90% of target in a 1:1 molar ratio by 60 min;

FIG. 8A and **FIG. 8B** show A_{2B} adenosine receptor ribozyme reduces NECA-stimulated VEGF synthesis and cell proliferation in HREC. Cells were stimulated with 10 μ mol/L NECA alone (◆), or NECA plus 1 μ mol/L of either a mixed 37-mer oligoribonucleotide (sham, ■) or A_{2B} ribozyme (▲). Both the amount of VEGF secreted into the medium (top) and the degree of proliferation (bottom) were decreased by the ribozyme, and not by the sham oligonucleotide control; and

FIG. 9 shows adenosine receptor antagonists reduce the degree of retinal neovascularization in the mouse pup model of oxygen-induced retinopathy. Daily IP injections of antagonists (30 mg/Kg body weight) resulted in a 54% to 70% reduction compared to untreated controls. The

number of eyes examined for each condition was at least 16. *Significantly different ($p < 0.05$) from uninjected.

FIG. 10 shows the number of neovascular nuclei counted per eye section for both the uninjected and AAV-IGF1R Rz1 injected eyes. Helix IV is at least 6 bases in length. The underlined bases can be any RNA tetraloop of the form ${}^5\text{GNRA}{}^3$ or UUCG, where N is any nucleotide and R is G or A. N can be any ribonucleotide (A, C, G or U) and N' is the complementary nucleotide. Y is a pyrimidine. H is any nucleotide but guanosine (A, C or U). B is any nucleotide but adenosine (G, C or U). V is the complement of B (G, C or A).

FIG. 11 shows a schematic illustration of a representative hairpin ribozyme molecule of the present invention (SEQ ID NO:105, SEQ ID NO:106). In particular, FIG. 11 shows a general hammerhead ribozyme structure. The italicized positions are constant. The stem may be any 4 or 5 base double stranded helix with a ${}^5\text{G-C}{}^3$ base pair at the top of the stem as drawn. Helix IV is at least 6 bases in length. The underlined bases can be any RNA tetraloop of the form ${}^5\text{GNRA}{}^3$ or UUCG, where N is any nucleotide and R is G or A. N can be any ribonucleotide (A, C, G or & and N' is the complementary nucleotide. Y is a pyrimidine. H is any nucleotide but guanosine (A, C or U). B is any nucleotide but adenosine (G, C or U). V is the complement of B (G, C or A).

FIG. 12 shows a schematic illustration of a representative hammerhead ribozyme molecule of the present invention (SEQ ID NO:107). The sequences of the arms may vary, as shown in Tables 4-8. The italicized positions are constant. The stem may be any 4 or 5 base double stranded helix with a ${}^5\text{G-C}{}^3$ base pair at the top of the stem as drawn. Underlined nucleotides in loop may be ${}^5\text{UUCG}{}^3$ or ${}^5\text{GNRA}{}^3$, where N is any nucleotide and R is a purine nucleotide.

5.2.4 ADENOSINE A_{2B} RECEPTOR REQUIRED FOR HREC ERK ACTIVATION

NECA (1 nmol/L – 10 μ mol/L) induced a transient activation of ERK which peaked at 5 min and desensitized within 20 min. The rate of desensitization was dependent on NECA concentration since higher doses of NECA produced a more rapid desensitization (FIGS. 3A-3B). The A₁-selective agonist CPA was also capable of stimulating ERK (FIGS. 4A-4C), however the A_{2A}-selective agonist CGS did not activate ERK. In order to determine the intracellular signaling pathways activated by NECA that regulate ERK activity, we pretreated cells for 30 min with the ERK/MPAK kinase (MEK) inhibitor PD98059 or the PKA inhibitor H-89 and stimulated with NECA for 5 min. PD98059 abolished ERK activation, while H-89 increased basal ERK activation (FIG. 5). H-89 did not block NECA-stimulated ERK activation, suggesting that PKA is not involved in signaling from the adenosine receptor to ERK. The non-selective adenosine receptor antagonist XAC decreased ERK activation by high concentrations of NECA, but modestly increased ERK activation in control conditions and in response to 1 and 10 nM NECA. Interestingly, prolonged activation with NECA in the presence of XAC or SCH and CPX reduced the rate of ERK desensitization, suggesting that adenosine receptors are involved in both activation and desensitization of ERK.

Phosphorylation of cAMP response element binding protein (CREB) at Ser¹³³ was examined following NECA stimulation in order to determine whether activation of cAMP pathways by NECA occurred independently of ERK activation. Cells were pretreated with PD98059 or H-89 and assayed for active CREB by western blot. PD98059 did not alter CREB activation, however both H-89 and XAC blocked CREB phosphorylation. These data indicate that ERK activation by NECA occurs independently of the cAMP response (FIG. 5).

Enprofylline and JW V108 exhibit greater selectivity for the A_{2B} receptor. Cells were pretreated with both antagonists for 10 min and stimulated with increasing concentrations of NECA. Enprofylline completely abolished ERK activation, while JW V108 inhibited ERK activation at all concentrations except for 10 μ M. These data suggest that ERK activation occurs through both the A_{2B} and A₁ receptors, but not the A_{2A} receptor (FIG. 6). These data support a role for adenosine in the activation of ERK that may then induce the phosphorylation of HIF 1- α .

5.3 EXAMPLE 3 – DEVELOPMENT AND TESTING OF RIBOZYME TARGETING A_{2B} ADENOSINE RECEPTOR mRNA

The cleavage site of the A_{2B} antisense, between nucleotides 183 and 184, was demonstrated to be accessible within the secondary structure of the native mRNA by the antisense studies. A hammerhead ribozyme designed to cleave this message was then synthesized along with a 14-nucleotide target sequence (FIG. 7A). This target was end-labeled in a standard kinase reaction with ³²P, then incubated along with ribozyme (1:1 molar ratio) for 1, 2, 3, 4, 5, 10, 30, 60, 120 and 180 min. Nearly 90% of target was cleaved by 60 min (FIG. 7C), demonstrating the efficacy and rapid action of this ribozyme in a cell-free assay system. The ribozyme's effects on HREC proliferation and VEGF synthesis in response to adenosine receptor activation was examined. HRECs were plated in serum-free medium overnight to adhere and make them quiescent. Unattached cells were then removed by washing with Hank's balanced salt solution (HBSS). The cells were then incubated with 1 U/mL adenosine deaminase (ADA) for 20 min, after which was added either medium alone, 1 μmol/L A_{2B} receptor ribozyme, or 1 μmol/L of a synthetic mixed oligonucleotide of the same length as the ribozyme, all of which contained 10 μmol/L NECA. Cells were then incubated for a total of seven days. Sampling occurred every 24 hr as follows. Conditioned medium was collected and stored at -70°C until the end of the assay, after which it was analyzed for VEGF using a commercially available ELISA. The cells were enzymatically dissociated from the wells and counted using a Coulter counter. These latter results were then used to normalize the VEGF data to a constant cell number. FIGS. 8A-8B show that cells treated with ribozyme express up to 60% less VEGF protein in response to NECA than do either untreated cells or cells treated with sham oligonucleotide. Similarly, these same cells exhibited a 50% reduction in proliferation 7 days after NECA stimulation when exposed to ribozyme compared to control.

TABLE 4
ILLUSTRATIVE HAIRPIN RIBOZYME TARGETS OF THE PRESENT INVENTION

RIBOZYME	SEQUENCE	SEQ ID NO:	REFERENCE
	<div> <div> <div>Cleavage site</div> <div>Helix II</div> <div>Helix I</div> </div> <div>↓</div> </div>		
ROD OPSIN mRNA-SPECIFIC:			
P23L target:	acgc a gcc	ucuuug-3' SEQ ID NO:3	Berson et al., 1991
Ribozyme arms:	ugcg aaga	agaagc-5' SEQ ID NO:108	
F45L target:	acau g guu	cugcug	Sung et al., 1991
Ribozyme arms:	ugug aaga	gacgac	
G51A target:	ugcu g gcc	uucccc	Macke et al., 1993
Ribozyme arms:	acgg aaga	aagggg	
G51G target:	ugcu g guc	uucccc	Dryja et al., 1991
Ribozyme arms:	acgg aaga	aagggg	
P53R target:	gcug g gcu	uccggc	Inglehearn et al., 1992
Ribozyme arms:	cgac aaga	aggccg	

	Q64stop target:	ucac	c guc	uagcac	SEQ ID NO:8	Macke et al., 1993
	Ribozyme arms:	agug	aaga	aucgug	SEQ ID NO:113	
	G90D target:	aggu	g gcu	ucacca	SEQ ID NO:9	Sieving et al., 1992
5	Ribozyme arms:	uccg	aaga	aguggu	SEQ ID NO:114	
	G106W target	uucu	g gcc	ccacag	SEQ ID NO:10	Sung et al., 1991
	Ribozyme arms:	aagg	aaga	gguguc	SEQ ID NO:115	
10	G114D target:	ugga	g gac	uucuuu	SEQ ID NO:11	Vaithinathan et al., 1994
	Ribozyme arms:	accu	aaga	aagaaa	SEQ ID NO:116	
	R135L target:	aucg	a guu	guacgu	SEQ ID NO:12	Jacobson et al., 1991
	Ribozyme arms:	uagc	aaga	caugca	SEQ ID NO:117	
15	R135P target:	aucg	a gcc	guacgu	SEQ ID NO:13	Rodriguez et al., 1993
	Ribozyme arms:	uagc	aaga	caugca	SEQ ID NO:118	
	P180A target:	acau	c gcc	gagggc	SEQ ID NO:14	Daiger et al., 1995
20	Ribozyme arms:	ugug	aaga	cucccg	SEQ ID NO:119	

D190G target: aauc g gcu acuaca SEQ ID NO:15 Dryja et al., 1991
 Ribozyme arms: uuag aaga ugaugu SEQ ID NO:120

H211R target: ucgu g guc cgcuuc SEQ ID NO:16 Macke et al., 1993
 Ribozyme arms: agcg aaga gcgaag SEQ ID NO:121

H211P target: ucgu g guc cccuuc SEQ ID NO:17 Macke et al., 1993
 Ribozyme arms: agcg aaga gggaag SEQ ID NO:122

F220C target: cauc u guu ucugcu SEQ ID NO:18 Bunge et al., 1993
 Ribozyme arms: guag aaga agacga SEQ ID NO:123

P347S target: aggu g gcc ucggcc SEQ ID NO:19 Dryja et al., 1990
 Ribozyme arms: uccg aaga agccgg SEQ ID NO:124

TABLE 5
ILLUSTRATIVE HAMMERHEAD RIBOZYME TARGETS OF THE PRESENT INVENTION

RIBOZYME	SEQUENCE	SEQ ID NO:	REFERENCE
5	Target reads 5' to 3' ribozyme reads 3' to 5'		
ROD OPSIN MRNA-SPECIFIC:			
P23H target:	gccacuu cgagua	SEQ ID NO:20	Berson et al., 1991
ribozyme arms:	cgguga gcucau	SEQ ID NO:125	
P23L target:	gccucuu cgagua	SEQ ID NO:21	Dryja et al., 1991
ribozyme arms:	cggaga gcucau	SEQ ID NO:126	
Q28H target:	cacacua cuaccu	SEQ ID NO:22	Bunge et al., 1993
ribozyme arms:	guguga gagggga	SEQ ID NO:127	
F45L target:	aug <u>g</u> uuc ugcuga	SEQ ID NO:23	Sung et al., 1991
ribozyme arms:	uaccaa acgacu	SEQ ID NO:128	
L46R target:	auguuuc g gcuga	SEQ ID NO:24	Rodriguez et al., 1993
ribozyme arms:	uacaaa ccgacu	SEQ ID NO:129	

G51R target:	ugcgcuu ccccau	SEQ ID NO:25	Dryja et al., 1992
ribozyme arms:	acgcga ggggua	SEQ ID NO:130	
G51A target:	uggccuu ccccau	SEQ ID NO:26	Macke et al., 1993
ribozyme arms:	accgga ggggua	SEQ ID NO:131	
G51V target:	uggucuu ccccau	SEQ ID NO:27	Dryja et al., 1991
ribozyme arms:	accaga ggggua	SEQ ID NO:132	
P53R target:	ugggcuu ccgc <u>cau</u>	SEQ ID NO:28	Inglehearn et al., 1992
ribozyme arms:	acccga ggcgua	SEQ ID NO:133	
T58R target:	cuuccuc aggcuc	SEQ ID NO:29	Bunge et al., 1993
ribozyme arms:	gaagga uccgag	SEQ ID NO:134	
T58R target:	caaggcuc uacguc	SEQ ID NO:30	Bunge et al., 1993
ribozyme arms:	guccga augcag	SEQ ID NO:135	
Q64stop target:	caccguc uagcac	SEQ ID NO:31	Macke et al., 1993
ribozyme arms:	guggca aucgug	SEQ ID NO:136	

	Q64stop target:	ccgucua gcacaa	SEQ ID NO:32	Macke et al., 1993
	ribozyme arms:	ggcaga cguguu	SEQ ID NO:137	
)68-71 target:	ugaacua cauccu	SEQ ID NO:33	Keen et al., 1991
5	ribozyme arms:	acuuga guagga	SEQ ID NO:138	
	V87D target:	ggaccua gguggc	SEQ ID NO:34	Sung et al., 1991
	ribozyme arms:	ccugga ccaccg	SEQ ID NO:139	
10	G90D target:	gugacuu caccag	SEQ ID NO:35	Sieving et al., 1992
	ribozyme arms:	cacuga gugguc	SEQ ID NO:140	
	G106W target:	cgucuuc uggccc	SEQ ID NO:36	Sung et al., 1991
	ribozyme arms:	gcagaa accggg	SEQ ID NO:141	
15	C110Y target:	caggaua caauuu	SEQ ID NO:37	Dryja et al., 1992
	ribozyme arms:	guccua guuaaa	SEQ ID NO:142	
	G114D target:	aggacuu cuuugc	SEQ ID NO:38	Vaithinathan et al., 1994
20	ribozyme arms:	uccuga gaaacg	SEQ ID NO:143	

R135G target:	aggggua cguggu	SEQ ID NO:39	Bunge et al., 1993
ribozyme arms:	ucccca gcacca	SEQ ID NO:144	
R135L target:	aguggua cguggu	SEQ ID NO:40	Andreasson et al., 1992
5 ribozyme arms:	ucacca gcacca	SEQ ID NO:145	
R135L target:	aguugua cguggu	SEQ ID NO:41	Jacobson et al., 1991
ribozyme arms:	ucaaca gcacca	SEQ ID NO:146	
10 R135P target:	agccgua cguggu	SEQ ID NO:42	Rodriguez et al., 1993
ribozyme arms:	ucggca gcacca	SEQ ID NO:147	
C140S target:	ugguguc uaagcc	SEQ ID NO:43	Macke et al., 1993
ribozyme arms:	accaca auucgg	SEQ ID NO:148	
P171L target:	accccuu cucgcc	SEQ ID NO:44	Dryja et al., 1991
ribozyme arms:	ugggga gagcgg	SEQ ID NO:149	
P171L target:	ccuacuc gccggc	SEQ ID NO:45	Dryja et al., 1991
20 ribozyme arms:	ggauga cggccg	SEQ ID NO:150	

P171S target:	cacccuc acucgc	SEQ ID NO:46	Stone et al., 1993
ribozyme arms:	guggga ugagcg	SEQ ID NO:151	
Y178C target:	gugcauc cccgag	SEQ ID NO:47	Farrar et al., 1991
5 ribozyme arms:	cacgua gggcuc	SEQ ID NO:152	
P180A target:	guacauc gccgag	SEQ ID NO:48	Daiger et al., 1995
ribozyme arms:	caagua cggcuc	SEQ ID NO:153	
10 C187Y target:	gcucgua uggaau	SEQ ID NO:49	Nathans et al., 1993
ribozyme arms:	cgagca accuua	SEQ ID NO:154	
G188R target:	ucgugua gaauca	SEQ ID NO:50	Dryja et al., 1991
ribozyme arms:	agcaca cuuagc	SEQ ID NO:155	
D190G target	uggaauca ggcua	SEQ ID NO:51	Dryja et al., 1991
ribozyme arms:	accuua ccgaug	SEQ ID NO:156	
D190Y target:	gaauca cuacua	SEQ ID NO:52	Fishman et al., 1992
20 ribozyme arms:	cuuaga gaugau	SEQ ID NO:157	

M207R target:	cagguuc gugguc	SEQ ID NO:53	Farrar et al., 1992
ribozyme arms:	guccaa caccag	SEQ ID NO:158	
H211R target:	cgugguc cgcuuc	SEQ ID NO:54	Macke et al., 1993
ribozyme arms:	gcacca gcgaag	SEQ ID NO:159	
H211P target:	cgugguc cccuuc	SEQ ID NO:55	Macke et al., 1993
ribozyme arms:	gcacca gggaag	SEQ ID NO:160	
C264X target:	ccugaau ugggug	SEQ ID NO:56	Vaithinathan et al., 1993
ribozyme arms:	ggacuua acccac	SEQ ID NO:161	
P267L target:	ggugcuc uacgcc	SEQ ID NO:57	Fishman et al., 1992
ribozyme arms:	ccacga augcgg	SEQ ID NO:162	
F220C target:	uaucauc uguuuc	SEQ ID NO:58	Bunge et al., 1993
ribozyme arms:	auagua acaaag	SEQ ID NO:163	
F220C target:	cuguuuc ugcuaa	SEQ ID NO:59	Bunge et al., 1993
ribozyme arms:	gacaaa acgaau	SEQ ID NO:164	

C222R target:	ucuuuuc cgcuau	SEQ ID NO:60	Bunge et al., 1993
ribozyme arms:	agacaa gcgaau	SEQ ID NO:165	
A292E target:	agaguuc uuugcc	SEQ ID NO:61	Dryja et al., 1993
ribozyme arms:	ucucaa aaacgg	SEQ ID NO:166	
Q344stop target:	cgagcua gguggc	SEQ ID NO:62	Sung et al., 1991
ribozyme arms:	gcucga ccaccu	SEQ ID NO:167	
P347S target:	uggccuc ggccua	SEQ ID NO:63	Dryja et al., 1990
ribozyme arms:	accgga cgggau	SEQ ID NO:168	
RP1 MRNA-SPECIFIC:			
R677stop target:	aaaaaauc uugaca	SEQ ID NO:64	Pierce et al., 1999
ribozyme arms:	uuuuuua aacugu	SEQ ID NO:169	
RDS/PERIPHERIN MRNA-SPECIFIC:			
C118 target:	ggcucuc ugcuuuc	SEQ ID NO:65	Farrar et al., 1991
ribozyme arms:	ccgaga acgaaaag	SEQ ID NO:170	
R172Q target:	gguuuuc aggacu	SEQ ID NO:66	Wells et al., 1993
ribozyme arms:	ccaaaa uccuga	SEQ ID NO:171	

R172W target:	gguuuuu	gggacu	SEQ ID NO:67	Wells et al., 1993
ribozyme arms:	ccaaaa	cccuga	SEQ ID NO:172	
5 P210R target:	guccguu	ucagcu	SEQ ID NO:68	Jackson et al., 1993
ribozyme arms:	caggca	agucga	SEQ ID NO:173	
C214S target:	gcugcuc	caaucc	SEQ ID NO:69	Keen and Inglehearn, 1996
ribozyme arms:	cgacga	guuagg	SEQ ID NO:174	
P216L target:	aauc <u>u</u> ua	gcucgc	SEQ ID NO:70	Kajiware et al., 1991
ribozyme arms:	uuagaa	cgagca	SEQ ID NO:175	
P219 target:	cuagcuc	gc ggcc	SEQ ID NO:71	Kajiware et al., 1991
15 ribozyme arms:	gaucga	cgccgg	SEQ ID NO:176	

TABLE 6
ADDITIONAL ILLUSTRATIVE HAIRPIN RIBOZYME TARGETS OF THE PRESENT INVENTION

RIBOZYME	SEQUENCE	SEQ ID NO:	REFERENCE
<div>5</div> <div>HelixII <u>Cleavage site</u> Helix I</div> <div>↓</div>			
RDS/PERIPHERIN MRNA-SPECIFIC:			
10	C118 target: ucuc u gcu uucugc	SEQ ID NO:72	Farrar et al., 1991
	Ribozyme arms: agag aaga aagacg	SEQ ID NO:177	
	R172W target: caac g guu uuuggg	SEQ ID NO:73	Wells et al., 1993
	Ribozyme arms: guug aaga aaaccc	SEQ ID NO:178	
15	P210R target: cguc c guu ucagcu	SEQ ID NO:74	Jackson et al., 1993
	Ribozyme arms: gcag aaga agucga	SEQ ID NO:179	
	C214S target: cagc u gcu cccauc	SEQ ID NO:75	Keen and Inglehearn 1996
	Ribozyme arms: gucg aaga gguuag	SEQ ID NO:180	
20	P216L target: ucuu a gcu cgccac	SEQ ID NO:76	Kajiware et al., 1991
	Ribozyme arms: agag aaga gcggug	SEQ ID NO:181	

P219 target: uccu a gcu cgccgc SEQ ID NO:77 Kajiwara et al., 1991

Ribozyme arms: aggg aaga gcgccg SEQ ID NO:182